REMARKS

Claims 1-12 are pending in the application, claims 13-20 are withdrawn, claims 21-36 are cancelled, and new claim 37 and 38 have been introduced. Claims 6 and 12 are rejected under 35 USC 112, second paragraph as being indefinite. In order to expedite prosecution, applicant hereby cancels claims 6 and 12. Claims 1-5 and 7-11 are rejected under 35 USC 103(a) as being unpatentable over Heath et al (US 5668152) in view of Cornford et al (AJP, v. 143, No. 1 (1999) 137-1244). In order to expedite prosecution, applicant hereby cancels claims 2-4 and claims 8-10, and amends claims 1 and 7. New claims 37 and 38 have been introduced and basis for these claims can be found at least in the specification on page 3, lines 11-29 and particularly lines 28-29.

In view of the reasons set forth below, it is submitted that the present rejection of the remaining claims is improper and should be withdrawn. Reconsideration and reexamination of the present application in view of the amendments and remarks presented herein is respectfully requested.

Rejection under 35 USC §112-Indefiniteness

In view of the cancellation of claims 6 and 12, this rejection is rendered moot.

Rejection under 35 USC §103(a)

Claims 1-5 and 7-11 are rejected under 35 USC 103(a) as being unpatentable over Heath et al (US 5668152) in view of Cornford et al (AJP, v. 143, No. 1 (1999) 137-144). In view of the cancellation of claims 2-4 and claims 8-10, the rejection of these claims is rendered moot. In view of the reasons set forth below, it is submitted that the present rejection of the remaining claims (i.e., 1, 5, 7, and 11) is improper and should be withdrawn. The Examiner asserts that:

> "Heath et al teaches working examples within the instant claims, such as working example 50-52 (columns 45-46) with favorable IC50 values, for the purpose of being protein kinase C inhibitors (abstract). Graff (sic) also teaches the use of protein kinase C inhibitors for the treatment of cancers (column 12 lines 25-32)." (Office Action Dated October 16, 2008)

Applicant respectfully submits that this argument under represents the state of the art of PKC biochemistry and inhibitor pharmacology as disclosed in the prior art document. At the time of Heath, the skilled artisan was well aware of at least ten PKC isozymes (column 1 lines 9-17) and the differential pharmaceutical and toxicological roles of these isozymes (column 1 lines 45-67 and column 2 lines 1-6). Addressing the inhibition of PKC without reference to the specific isozyme(s) being inhibited does not represent the level of skill in the

art at the time of Heath. Heath et al teaches that PKC-β1 and PKC-β2 isozyme selective inhibitors may be useful for treating PKC-β1 and PKC-β2 isozyme mediated disease (column 11 lines 66-77 and column 12 lines 1-5) with cancer mentioned in a list of diseases (columns 12 lines 25-32) and no specific cancer recited. Thus, at most, Heath et al teaches a skilled artisan that the compounds disclosed therein may be useful for treating PKC-β1 and PKC-β2 isozyme mediated cancers with a PKC-β1 and PKC-β2 isozyme selective agent.

The Examiner further asserts that:

> "Cornford et al teaches in prostate cancer, PKC activity was vital for the growth of androgen-independent prostate cells" (page 138, about lines 15-19).

Applicants respectfully submit that this quote from Cornford overstates the teaching of the reference as a whole. In context, the quote from Cornford reads:

> "Interest in the role of PKC in prostate cancer was stimulated when it was shown that PKC activity was vital for growth of androgen-independent prostate cells…" (page 138, about lines 14-17, citing Krongrad et al., Cancer Res. 1994, 54:6073-6077)

To support this conclusion, Krongrad utilized chelerythrine, an isoform nonspecific PKC inhibitor (Kongrad page 6075, column 1, about lines 3-4). Kongrad goes on to diminish the impact of this statement:

> "This finding suggests that regardless of which signal modulator or which gene-regulatory mechanism underlies phorbol esters insensitivity in androgen-independent cancer cells, PKC <u>may</u> be biologically relevant and in fact <u>may</u> be required for cell viability. (Kongrad page 6076, column 1, about lines 29-column 2, lines 1-2)

At the time of Kongrad, it was not technically feasible to measure isoform-specific PKC activity (Kongrad page 6076, column 1, about lines 21-22). Cornford addresses this technical feasibility problem by specifically studying not total PKC expression, but the expression of each PKC isoform in prostatic adenocarcinomas.

Cornford et al teaches the comparative expression of PKC isoforms in early prostatic adenocarcinomas and age matched nonneoplastic prostate tissue. Cornford teaches that

> "The most significant findings were a <u>decrease</u> in PKC-β expression in early neoplasia when compared to benign epithelium ($P < 0.0001$), together with a reciprocal increase in expression of PKC-ε ($P < 0.0001$). Detectable levels of PKC-α and PKC-ζ were also significantly increased in the cancers ($P = 0.045$ and $P = 0.015$ respectively) but did not correlate with either PKC-β or PKC-ε for individual cases." (see abstract, emphasis added).

Having clarified the scope and content of the cited prior art and the level of skill in the pertinent art, the Applicant respectfully submits that a skilled artisan would not be motivated to combine the cited prior art references to arrive at the present invention as claimed. A skilled artisan reviewing Cornford would be looking for differential expression of the PKC isoforms in prostatic adenocarcinomas and age matched nonneoplastic prostate tissue and would, potentially, be motivated to treat a significant increase in expression of a particular isozyme with an inhibitor of that isozyme. As shown above, this would motivate a skilled artisan to look for either non-specific isozyme inhibitors such as chelerythrine or, at least, an inhibitor of PKC-ε, PKC-α, PKC-ζ or a combination of such. In conclusion, for the above reasons a skilled artisan would not be looking for compounds described as PKC-β1 and PKC-β2 isozyme selective inhibitors (teaching of Heath) and would not, reasonably, expect success in using such compounds for the treatment of prostate cancer. For all of the above reasons, the Applicants respectfully assert that data demonstrating the utility of a PKC-β1 and PKC-β2 isozyme selective inhibitors (as submitted in the 131 declaration dated July 3, 2008) in prostate cancer is unexpected.

Applicants further submit the following response to the Examiners obviousness assertions. First, the Examiner alleges that the difference in PKC isozyme activity between compounds 49 and 52 would account for the difference in apoptosis activity submitted in the declaration. The Applicants respond that this is not an accurate assessment of the data. PKC-β1 and PKC-β2 isozyme activity would not be expected to induce apoptosis in androgen-independent prostatic adenocarcinoma. As described in the specification discussing prostatic adenocarcinoma, "Activation of the AKT pathway can suppress the apoptotic response, undermine cell cycle control, and selectively enhance the production of key growth and survival factors." (Page 3 at lines 22-24). As indicated in the declaration, treatment of androgen-independent prostatic adenocarcinoma cell lines (DU145 and $CWR22_{RV1}$) with compound 49 demonstrated no increase in apoptosis from baseline whereas compound 52 demonstrated a robust induction of apoptosis in this assay. It is the AKT pathway inhibition, and not the PKC isozyme inhibition, that is associated with inducing apoptosis. For this reason, Applicants respectfully request reexamination of the declaration data in light of the above arguments.

Second, the Examiner alleges that the in vitro data submitted in the declaration is unpredictive citing Suggitt and Bibby, *Clinical Cancer Research*, 2005, Vol 11, 971-981. Applicants respectfully submit that the cited reference is quoted out of context. The topic of Suggitt and Bibby is the traditional cancer cell line panels screened for traditional cytotoxic

agents. The endpoints for these assays are measures of indiscriminant cell killing. The quotes cited by the Examiner follow the description of these assays as such and thus summarize the state of the art with regard to these assays alone. The data presented in the declaration is of induction of apoptosis and not indiscriminant cytotoxicity as discussed in Suggitt and Bibby. Applicants submit that the data disclosed in the declaration have no relation to the assays discussed in Suggitt and Bibby and the Examiners objection to the data on this ground is improper and should be withdrawn. For this reason, Applicants respectfully request reexamination of the declaration data in light of the above arguments.

Finally, the Examiner alleges that the data presented is not commensurate in scope with the claims. While Applicant respectfully disagrees, in order to expedite prosecution, Applicants have amended the claims to a single species to make them more commensurate in scope with the data. For this reason, Applicants respectfully request reexamination of the declaration data in light of the above arguments.

SUMMARY

For all of the foregoing reasons, Applicants respectfully submit that the present rejection is improper and should be withdrawn. Reconsideration and reexamination of the present application is view of the amendments and remarks presented herein is respectfully requested.

Please charge any fees or credit any overpayment in connection with this application which may be required by this or any related paper to Deposit Account No. 05-0840.

If the Examiner has any questions, or would like to discuss any matters in connection with this application, he or she is invited to contact the undersigned at (317) 276-0307.

Respectfully submitted,

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